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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte JACQUES DUMAS,
UDAY KHIRE, TIMOTHY B. LOWINGER,
HOLGER PAULSEN, BERND RIEDL, WILLIAM J. SCOTT,
ROGER A. SMITH, JILL WOOD, HOLIA HATOUM-MOKDAD,
WENDY LEE, ANIKO REDMAN, JEFFREY JOHNSON,
and ROBERT SIBLEY

Appeal 2010-009254
Application 09/458,014
Technology Center 1600

Before TONI R. SCHEINER, FRANCISCO C. PRATS, and
JEFFREY N. FREDMAN, Administrative Patent Judges.

PRATS, Administrative Patent Judge.

DECISION ON APPEAL

This appeal under 35 U.S.C. § 134 involves claims to methods of treating rheumatoid arthritis. The Examiner entered a rejection for lack of enablement, as well as a number of provisional rejections for obviousness-type double patenting.

We have jurisdiction under 35 U.S.C. § 6(b). We reverse the enablement rejection, but decline to reach the provisional double patenting rejections.

STATEMENT OF THE CASE

Appellants' invention includes compounds, "generally described as aryl ureas, including both aryl and heteroaryl analogues, which inhibit p38 mediated events and thus inhibit the production of cytokines (such as TNFα, IL-1 and IL-8) and proteolytic enzymes (such as MMP-1 [matrix-destroying metalloprotease 1] and MMP-3)" (Spec. 6).

Accordingly, the Specification also discloses therapeutic methods involving administration of the inventive compounds:

> The invention also provides a method of treating a cytokine mediated disease state in humans or mammals, wherein the cytokine is one whose production is affected by p38. Examples of such cytokines include, but are not limited to TNFα, IL-1 and IL-8. The invention also provides a method of treating a protease mediated disease state in humans or mammals, wherein the protease is one whose production is affected by p38. Examples of such proteases include, but are not limited to collagenase (MMP-1) and stromelysin (MMP-3).

(Id.) Thus, Appellants' compounds are "useful therapeutic agents for such acute and chronic inflammatory and/or immunomodulatory diseases as rheumatoid arthritis" (id.).

Claims 1-4, 8, 28, 30, 38, 44, 45, 50, 51, 55, and 58 stand rejected and appealed (App. Br. 2).

Claim 1 is representative and recites "[a] method for the treatment of rheumatoid arthritis, comprising administering a compound of formula I" (id. at 11).

Formula I has the following structure (id.):

I

Claim 1 specifies that moiety "B" can be any one of a set of numerous different substituents, including "a substituted or unsubstituted, up to tricyclic, aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 5- or 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur" (id.).

Claim 1 further specifies that

> A is a heteroaryl moiety selected from the group consisting of
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> 
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> wherein R^1 is selected from the group consisting of halogen, C_3-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{13} heteroaryl, C_{6-14} aryl, C_{7-24} alkaryl, up to per-halosubstituted C_1-C_{10} alkyl, up to per- halosubstituted C_3-C_{10} cycloalkyl, up to per-halosubstituted C_1-C_{13} heteroaryl, up to per- halosubstituted C_{6-14} aryl, and up to per-halosubstituted C_{7-24} alkaryl.

(Id. at 12.)

The following rejections[1] are before us for review:

(1) Claims 1-4, 8, 28, 30, 44-45, 50-51, and 55, provisionally rejected under the judicially created doctrine of obviousness-type double

[1] On page 3 of the Answer the Examiner listed provisional obviousness-type double patenting rejections over copending applications 09/838,286, 09/947,761, and 10/361,858, but later withdrew those rejections (Ans. 9).

patenting over claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426 (Ans. 3-4);

(2) Claims 1-4, 8, 28, 30, 44-45, 50-51, and 55, provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-69 of copending Application No. 10/848,567 (Ans. 3-4);

(3) Claims 1-4, 8, 28, 30, 44-45, 50-51, and 55, provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-34 and 37-41 of copending Application No. 11/932,548 (Ans. 3-4);

(4) Claims 1-4, 8, 28, 30, 44-45, 50-51, and 55, provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-16 of copending Application No. 12/181,032 (Ans. 3-4); and

(5) Claims 1-4, 8, 28, 30, 38, 44, 45, 50, 51, 55, and 58, under 35 U.S.C. § 112, first paragraph, for lack of enablement (Ans. 4-9).

ENABLEMENT

Applying the criteria set forth in In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988), the Examiner finds that, while TNFα has been linked to a number of inflammatory diseases, there is "no indication that such a link actually translates to treatment of the disease. Therefore, the same argument can be applied to p38 inhibition. Accordingly, the same argument is applied to rheumatoid arthritis" (Ans. 5).

Thus, the Examiner reasons, even assuming that "an inhibition of p38 would lead to the desired inhibition of TNFα, a link between TNFα

production and rheumatoid arthritis doesn't mean that any inhibition of TNFα would treat rheumatoid arthritis. It is further noted that the specification likewise indicates that TNFα production is linked to numerous other diseases" (*id.*).

The Examiner further notes that "the claims encompass any urea illustrated by the broad generic structure of formula I" (*id.* at 6). Accordingly, the Examiner finds, the "nature of the invention is complex in that it potentially encompasses a vast number of compounds in excess of 100 million compounds" (*id.*).

The Examiner finds that, because the Specification's *in vivo* testing method "was not performed on subjects with any diseases or disorders" an ordinary artisan "would be forced to perform an exhaustive search for the embodiments of any drug having the function recited in the instant claims suitable to practice the invention" (*id.*). The Examiner further finds that the potential therapeutic effects of drug compounds are highly unpredictable, given potential toxicity issues and drug-drug interactions (*id.* at 7 (citing Goodman & Gilman's 51)).[2]

The Examiner further finds that the Specification does not provide any working examples of treating rheumatoid arthritis with any compound encompassed by the claims, and notes that the Specification provides no raw data with respect to the disclosed *in vitro* p38 inhibition assay and *in vivo* mouse TNFα inhibition assay (*id.* at 8). Thus, the Examiner concludes, given the lack of adequate guidance, Appellants' Specification fails to provide an enabling disclosure (*id.* at 8-9).

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[2] GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (McGraw-Hill 1996).

Appellants initially point out that, contrary to several assertions by the Examiner, the claims are limited to treating a single disorder, rheumatoid arthritis (App. Br. 5). Thus, Appellants urge, given the art-recognized connection between p38 and rheumatoid arthritis, and the related TNFα and MMP activities, an ordinary artisan would have recognized that the disclosed compounds' capacities to inhibit p38 would have rendered them suitable for treating the claimed disorder, as asserted in the Specification (*id.* at 5-6).

Appellants also contend that, as asserted in the Specification, at least one p38 inhibitor has been shown to have activity in an animal model for arthritis (*id.* at 6 (citing Badger)).[3] In contrast, Appellants assert, the Examiner has not presented "any evidence . . . to refute the findings or conclusions made in any of the publications cited in the specification" nor has the Examiner presented any evidence "that any of the methods claimed would not be effective in treating rheumatoid arthritis. Only unsupported allegations and conclusions regarding the state of the art are provided" (*id.*).

Thus, Appellants urge, the Examiner has not met the "burden of establishing that the disclosure does not enable one skilled in the art to perform the methods claimed. Instead of relying on proper probative evidence, the rejection is improperly based on bare allegations and conclusions" (*id.* at 8).

We conclude that Appellants have the better position.

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[3] Badger et al., Pharmacological Profile of SB 203580, a Selective Inhibitor of Cytokine Suppressive Binding Protein/p38 Kinase, in Animal Models of Arthritis, Bone Resorption, Endotoxin Shock and Immune Function, 279 JOURNAL OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS 1453-1461 (1996).

As Appellants point out, it is well settled that when making an enablement rejection, "it is incumbent upon the Patent Office . . . to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971).

As stated in In re Oetiker, 977 F.2d 1443, 1445 (Fed. Cir. 1992):

> [T]he examiner bears the initial burden . . . of presenting a prima facie case of unpatentability. . . .
>
> After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of argument.

In the instant case, we find that the preponderance of the evidence does not support the Examiner's prima facie case of non-enablement.

The Specification asserts that "[c]linical studies have linked TNFα production and/or signaling to a number of diseases including rheumatoid arthritis" and cites a publication to support that assertion (Spec. 2). The Specification also asserts that rheumatoid arthritis is among diseases "thought to be mediated by excess or undesired matrix-destroying metalloprotease (MMP) activity or by an imbalance in the ratio of MMPs to the tissue inhibitors of metalloproteinases" and cites several publications to support that assertion (*id.* at 4).

The Specification further asserts that "[i]nhibition of p38 has been shown to inhibit both cytokine production (eg., TNFα, IL-1, IL-6, IL-8) and proteolytic enzyme production (eg., MMP-1, MMP-3) *in vitro* and/or *in vivo*" (*id.* at 2). The Specification thus reasons that, "[b]ecause inhibition of

p38 leads to inhibition of TNFα production" (*id.* at 4), and "[b]ecause inhibition of p38 leads to inhibition of MMP production, p38 inhibitors will be useful in treatment of" rheumatoid arthritis (*id.* at 5).

The Specification then provides examples of how to synthesize the claimed compounds (*id.* at 31-103), and provides an *in vitro* p38 inhibition assay, which verified that "[a]ll compounds exemplified displayed p38 IC_{50s} of between 1 nM and 10μM (*id.* at 104). The Specification also provides an assay to measure the LPS-induced production of TNFα in mice (*id.*).

While the Examiner asserts that the linkage described in the Specification between p38 inhibition and inhibition of the cytokines and proteases involved in rheumatoid arthritis is insufficient to show that p38 inhibitors would be expected to treat rheumatoid arthritis, the Examiner has not pointed to any specific evidence to support this assertion. *See In re Marzocchi*, 439 F.2d at 224 (emphasis added):

> [I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure *and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement*."

Thus, the Examiner has not provided any actual evidence, such as a publication, suggesting that p38 inhibitors do not function in the manner asserted in the Specification, are inadequate for treating rheumatoid arthritis, or act unpredictably in models relevant to the disease. In contrast, in addition to the publications cited in the Specification, Appellants have provided evidence, in the form of the Badger reference, showing that at least one p38 inhibitor has activity in an animal model for arthritis (*see* App. Br. 18 (Evidence Appendix)).

> The Examiner responds:
>
> The Badger reference is an isolated reference that cannot be taken as the standard for the state of art concerning inhibition of p38 and the treatment of various diseases. The reference does not provide any evidence describing the activity of a pyridinyl imidazole p38 kinase inhibitor are applicable to the aryl ureas of the claimed formula I. Further, the abstract does not provide the missing guidance regarding how to determine which compounds of formula I that are found to inhibit p38 kinase activity do so in a manner sufficient to inhibit TNFα to a degree that results in the treatment of rheumatoid arthritis.

(Ans. 11.)

Again, however, the Examiner does support these assertions with any specific evidence suggesting that an ordinary artisan would have failed to consider Badger indicative of the state of art, particularly in light of the knowledge in the art as evidenced by the Specification. Nor has the Examiner provided an adequate evidence-based explanation as to why an ordinary artisan, aware of the link between p38 inhibition and TNFα/MMP inhibition, and aware of the link between rheumatoid arthritis and TNFα/MMP, would have had to resort to undue experimentation in order to treat rheumatoid arthritis with the claimed p38-inhibiting compounds.

We acknowledge Goodman & Gilman's disclosure that therapeutic methods can be unpredictable. However, given the teachings in the Specification and Badger's verification in an animal model, we are not persuaded that any unpredictability inherent in this art demonstrates a lack of enablement. Moreover, a claim does not lack enablement merely because it encompasses inoperative embodiments. Atlas Powder Co. v. E.I. du Pont De Nemours & Co., 750 F.2d 1569, 1576 (Fed. Cir. 1984).

We also acknowledge that the Specification does not contain a working example of treating a rheumatoid arthritis patient. However, as Appellants argue, "[working] examples are not required to satisfy section 112, first paragraph." In re Strahilevitz, 668 F.2d 1229, 1232 (CCPA 1982). For example, in Falko-Gunter Falkner v. Inglis, 448 F.3d 1357, 1365 (Fed. Cir. 2006), the court affirmed this Board's conclusion that claims to a modified pox virus vaccine were enabled, despite the fact that the specification focused on viruses other than pox virus, provided no examples directed to pox virus, and discussed pox virus only in general terms relating to the inventive disclosure. Moreover, as discussed above, at least one p38 inhibitor has been shown to be active in an animal model for arthritis.

In sum, considering the record as a whole, for the reasons discussed, we are not persuaded that the Examiner has met the burden of establishing a prima facie case of lack of enablement. We therefore reverse the Examiner's rejection of claims 1-4, 8, 28, 30, 38, 44, 45, 50, 51, 55, and 58, under 35 U.S.C. § 112, first paragraph.

OBVIOUSNESS-TYPE DOUBLE PATENTING

The Examiner provisionally rejected claims 1-4, 8, 28, 30, 44-45, 50-51, and 55, under the judicially created doctrine of obviousness-type double patenting over claims 1-13, 15-17, 20, 22-30 of copending Application No. 10/788,426; and also over claims 1-69 of copending Application No. 10/848,567; and also over claims 1-34 and 37-41 of copending Application No. 11/932,548; and also over claims 1-16 of copending Application No. 12/181,032 (Ans. 3-4).

In light of this Board's precedential decision in Ex Parte Moncla, 95 USPQ2d 1884 (BPAI 2010) (see also http://www.uspto.gov/ip/boards/bpai/decisions/prec/fd09006448.pdf), concluding it premature to address a provisional non-statutory double patenting rejection when all other remaining rejections had been reversed, we decline to address the merits of these rejections.

However, when prosecution resumes in this case, the Examiner should verify that none of the copending applications with overlapping subject matter have been allowed or matured into issued patents.

SUMMARY

We reverse the Examiner's rejection of claims 1-4, 8, 28, 30, 38, 44, 45, 50, 51, 55, and 58, under 35 U.S.C. § 112, first paragraph, for lack of enablement.

We decline to address the merits of the Examiner's provisional obviousness-type double patenting rejections.

REVERSED

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